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Fibrinogen in Traumatic Haemorrhage: A Narrative Review

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Abstract:

Haemorrhage in the setting of severe trauma is associated with significant morbidity and mortality. There is increasing awareness of the important role fibrinogen plays in traumatic haemorrhage. Fibrinogen levels fall precipitously in severe trauma and the resultant hypofibrinogenaemia is associated with poor outcomes. Hence, it has been postulated that early fibrinogen replacement in severe traumatic haemorrhage may improve outcomes, although, to date there is a paucity of high quality evidence to support this hypothesis. In addition there is controversy regarding the optimal method for fibrinogen supplementation. We review the current evidence regarding the role of fibrinogen in trauma, the rationale behind fibrinogen supplementation and discuss current research.

Abbreviations: A5 (A10) = amplitude of clot firmness 5 (10) minutes after CT, BW = body weight, CFT = clot formation time, Cryo = cryoprecipitate, CT = clotting time, DCR = damage control resuscitation, ED = Emergency Department, FC = fibrinogen concentrate, FibC = Clauss Fibrinogen, FFP = fresh frozen plasma, GCUH = Gold Coast University Hospital, Queensland, Australia, Hb = Hemoglobin, iCa = ionized Calcium, ICU = intensive care unit, MCF = maximum clot firmness, MHP = major haemorrhage protocol, OR = operating room, rPT = rapid Prothrombin Time, POC = Point of Care, PRBC = packed red blood cells, PT = Prothrombin Time SLT = standard laboratory test, Temp = core temperature, TIC = trauma-induced coagulopathy, TXA = tranexamic acid, VHA = viscoelastic hemostatic assays

Key Words: Trauma, Coagulopathy, Fibrinogen, Cryoprecipitate, Fibrinogen Concentrate, Massive Transfusion, Viscoelastic Haemostatic Assays.

Introduction:

Trauma is a leading cause of death worldwide in individuals aged 18-39 years and represents a major global health concern (1). Despite advances in trauma management, a significant proportion of these deaths are secondary to haemorrhage and preventable (2) (3) (4). In patients where surgical haemorrhage control is achieved, subsequent morbidity and mortality is often attributed to coagulopathy complicated by organ failure due to the effects of major haemorrhage and large volume blood product transfusion (5) (6) (7). Death related to major haemorrhage is potentially preventable and represents a target for mortality reduction strategies. There is increasing awareness regarding the critical role of fibrinogen in traumatic

haemorrhage. The objectives of this review are to examine the available evidence regarding fibrinogen in severe trauma and explore its potential role in management.

Methods:

A literature search was performed on major databases including PubMed, Medline, Embase, Web of Science and ClinicalTrials.gov. Search terms included “fibrinogen”, “trauma”, “transfusion protocols”, “massive transfusion”, “cryoprecipitate”, “fibrinogen concentrate”, “viscoelastic testing”, “ROTEM” and “TEG”. Titles and abstracts were reviewed and full text articles retrieved for inclusion if considered relevant. Additional articles were identified from reference lists of identified articles. Database searches were supplemented by private files/collections of the authors, and a grey literature search using Google scholar. Results are presented in a narrative form.

Role of Fibrinogen in Trauma Induced Coagulopathy:

Severe trauma may be complicated by a unique, complex and multifactorial coagulopathy – Trauma Induced Coagulopathy (TIC); of which the exact pathophysiological mechanisms are yet to be elucidated (8) (9) (10) (11). TIC is characterized by reduced clot strength related to hypo/dysfibrinogenaemia, platelet dysfunction, hyperfibrinolysis and endothelial dysfunction (12). Central to the proposed mechanism is the effect of direct tissue injury and hypoperfusion on the endothelium resulting in systemic anticoagulation and hyperfibrinolysis (13). TIC may subsequently be exacerbated by acidosis, hypothermia, haemodilution and factor consumption (14) While the exact mechanisms are debated, patients with TIC do

certainly have significantly increased transfusion requirements and mortality (15) (16).

The role of fibrinogen in maintaining effective haemostasis is widely accepted (17). Fibrinogen is a glycoprotein synthesised in the liver and is the key final component of the clotting cascade; forming fibrin – an insoluble protein that is the foundation of a stable clot (18). Fibrinogen is cleaved by Thrombin to fibrin monomers, which are polymerised and subsequently stabilised by activated Factor XIII to form a fibrin clot (19). Fibrinogen is also fundamental in the aggregation of activated platelets through the glycoprotein IIb/IIIa receptors. The healthy adult has a plasma fibrinogen concentration of between 2 to 4g/L (20).

In traumatic haemorrhage, there is increasing evidence supporting the important role fibrinogen plays in effective clot formation. Lower levels of fibrinogen and increased fibrinogen breakdown are key features of TIC (21) (22). Fibrinogen is the first factor to fall below reference values during bleeding and in trauma reaches critically low levels earlier than any other coagulation factors (23). This has been demonstrated in both the pre-hospital environment and early after arrival in the trauma unit prior to large volume fluid resuscitation (24) (25). In a number of studies the degree of hypofibrinogenaemia is strongly associated with injury severity (22) (26). This suggests fibrinogen deficiency is innately related to the primary and secondary physiological insults induced by severe trauma. Subsequently, further hypofibrinogenaemia occurs as a consequence of major blood loss, consumption, dilution, acidosis and hypothermia (27) (28) (29) (30). In addition, the fibrin strands that form in a low fibrinogen environment are more susceptible to fibrinolysis and a

number of studies report hypofibrinogenaemia in the presence of hyperfibrinolysis (31) (32) (33). Hyperfibrinolysis in the setting of severe trauma is a central component of TIC and although relatively rare is associated with poor outcomes (34) (35) (36). The association between hypofibrinogenaemia and worse outcomes in severe trauma has been well demonstrated although to date the pathophysiological mechanisms remain incompletely understood (22) (37) (38).

Major Haemorrhage Protocols (MHP):

Major Haemorrhage Protocols utilised by many trauma centres are activated once significant haemorrhage is suspected. In addition to rapid surgical control of haemorrhage, the MHP involves the empiric and early delivery of a predefined fixed-ratio transfusion of blood products (Plasma, Platelets and PRBC), in an attempt to ameliorate the coagulopathy associated with major haemorrhage and large volume blood transfusion (39) (40). MHP have been implemented in response to studies showing that in massive transfusion the inadequate replacement of coagulation factors is associated with poor outcomes (41). Whilst it is clear that the institution of a MHP does improve outcomes, the optimal ratio of blood components to PRBC remains the focus of considerable debate (42) (43) (44) (45) (46).

The PROMMTT study provided initial data to support a high product to PRBC transfusion ratios in trauma MHP (1:1:1 Plasma:Platelets:PRBC) (47). The survival advantage postulated to be due to earlier replacement of consumed factors mitigating the effect of TIC and that the replacement physiologically more closely approximates to what is being lost. However, even in high ratios the delivered

replacement is potentially dilute in terms of factors (39). The subsequent Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial reported no difference in survival between a 1:1:1 or 1:1:2 transfusion strategy but more patients in the 1:1:1 group achieved haemostasis and fewer died from exsanguination (48). A number of studies have reported that in patients receiving higher ratios there is an increase in the amount of plasma transfused and an increased incidence of transfusion-related adverse events without a survival benefit, however, these concerns were not confirmed in the PROPPR trial (49) (50) (51). Time to delivery of product replacement in PROPPR was rapidly achieved without significant wastage but this is dependent on having thawed product available 24 hours a day in either the trauma unit or blood bank (52). The impressive delivery of blood component therapy as described in the PROPPR trial may be difficult to translate into routine clinical practise (53). A recent study from Stanworth et al. reports widespread variations in patterns of blood product delivery across a number of trauma centres, with few patients receiving an ‘optimal’ product ratio (54).

Fibrinogen Replacement as part of a MHP:

Hypofibrinogenaemia after severe trauma is associated with increased risk of both massive transfusion and mortality (37) (55). It is postulated that early fibrinogen replacement may be efficacious in correction of coagulopathy, assist in haemorrhage control and decrease transfusion requirements (37) (56) (57) (58). Two studies from the military indicate that maintaining higher fibrinogen levels as part of a MHP is associated with improved survival (59) (60).

Empiric and early fixed ratio delivery of specific fibrinogen containing products is not standard practice in the majority of MHP. Whilst plasma does contain fibrinogen it is in a concentration and volume that is potentially too dilute in terms of adequacy of replacement. The mean fibrinogen concentration in plasma is approximately 2g/L and large volumes of plasma (+/- 30ml/Kg) are required to adequately supplement fibrinogen (61). In most MHP the transfusion of additional fibrinogen in the form of cryoprecipitate usually occurs only late in the protocol and in response to low plasma fibrinogen levels as measured by laboratory tests of plasma fibrinogen. There are inherent problems with this approach resulting in significant delays to effective administration of fibrinogen. In addition there is significant debate regarding at what level of plasma fibrinogen should trigger additional fibrinogen replacement. The majority of current guidelines would suggest that plasma fibrinogen levels of < 1 – 1.5g/l should trigger additional fibrinogen, however, this is not based on solid evidence (62) (63). Hagemo et al, have demonstrated an increased mortality in trauma patients with fibrinogen levels below 2.29g/l (22). In severe trauma fibrinogen levels should potentially be maintained at levels higher than currently recommended. The 2016 European Trauma Guidelines recommend fibrinogen supplementation if thromboelastometric signs of functional fibrinogen deficiency or plasma fibrinogen levels < 1.5 – 2g/l (64).

Fibrinogen can be replaced with: fibrinogen concentrate (FC), cryoprecipitate or plasma, each containing different amounts of fibrinogen: 20g/L, 8-16g/l and 2g/L, respectively, and therefore different volumes are required to achieve replacement (65). A study by Rourke et al. (37) demonstrated that standard protocol driven transfusion ratios were ineffective in maintaining fibrinogen levels and the addition of

cryoprecipitate was required. Khan et al. (66) showed that high dose plasma transfusion does not correct TIC and coagulation parameters only improve with plasma, cryoprecipitate and platelet transfusion with a combined high fibrinogen load. Chambers et al. (67) report that 1:1:1 MHP does not affect the frequency or duration of coagulopathy as measured by standard coagulation tests and hypofibrinogenaemia was almost always the first abnormality detected.

The PROMMTT study described wide variability in cryoprecipitate transfusion practices in 10 American Level 1 trauma centres; in those patients receiving cryoprecipitate the median time to transfusion was 2.7 hours and the majority of those patients who died of haemorrhage did not receive cryoprecipitate (68). These findings are supported by a recently published study from the UK investigating transfusion practices in traumatic haemorrhage - the median time to delivery of cryoprecipitate as part of a MHP was more than 2 hours and almost 50% of patients did not receive cryoprecipitate as part of their initial resuscitation (54). This is concerning, considering that the median time to death from haemorrhage is reported to be approximately 2.6 hours (48) (54).

The CRYOSTAT study, recently published by Curry et al. (69), demonstrated that the early administration of cryoprecipitate as part of a MHP is feasible in trauma patients. 85% of patients randomised to the Cryo arm received cryoprecipitate within 90 minutes and the median time to transfusion was 60 minutes. Additionally, fibrinogen levels were consistently higher throughout active haemorrhage in the Cryo arm.

The ideal trauma MHP remains elusive and a number of key questions remain unanswered. Amongst these are: 1) Which laboratory tests and what triggers should be used to guide resuscitation 2) What is the impact of early fibrinogen replacement on haemostasis and clinical outcomes (46).

Assessment of TIC: Standard Laboratory Tests (SLT)

The diagnosis of TIC is conventionally made using prothrombin time (PT) and activated partial thromboplastin time (APTT). These tests, performed on platelet poor plasma were developed to determine single factor deficiencies and effects of anticoagulant therapy. They are poor predictors of bleeding in trauma and due to time delay to result availability fail to provide contemporary information (70) (71). Neither the PT nor APTT give an indication of the fibrinogen contribution to clot strength or quality. There are number of laboratory test utilised to quantify plasma fibrinogen levels, the two most common are; Clauss Fibrinogen (FibC) and Prothrombin Time (PT) Derived Fibrinogen. In the FibC test, concentrated thrombin is added to dilute plasma, converting fibrinogen to fibrin and the clotting time is inversely proportional to the amount of fibrinogen. In the PT-Derived Fibrinogen the difference between baseline and maximum turbidity is proportional to fibrinogen concentration (72) (73). The tests should not be used interchangeably as there can be significant discrepancies between PT-derived fibrinogen and FibC (74). There can be significant variations in reproducibility and consistency in fibrinogen levels between laboratories utilising either test due to differences in; type of analyser, read out method (photo-optical or electromechanical), software and brand of assay used (75). The use of artificial colloids can also falsely elevate the fibrinogen level

reported by both tests (72) (76) (77). However, this is unlikely to be of major concern in Australia, where the use of artificial colloids is not usual standard practice. The major limitation in utilising either test for assessment of fibrinogen concentration in severe trauma is the time delay to result availability, which can be greater than 60 minutes (78). An emergency haemorrhage panel utilising standard laboratory tests (including fibrinogen) with modifications to sample centrifuging, assays and calibration ranges is reported to be available in approximately 20 minutes (79). However, this is not routinely available in Australia and may be difficult to implement into routine clinical practice.

Assessment of TIC: Viscoelastic Haemostatic Assays (VHA):

An alternative to SLT, utilises viscoelastic haemostatic assays (VHA) to rapidly identify coagulation defects and potentially guide targeted interventions (80) (81) (82) (83) (84). Two commercially available devices: TEG® (Haemonetics, Braintree, MA, USA) and ROTEM® (TEM International GmbH, Munich, Germany) are in widespread use; neither is superior and utilisation differs geographically (85) (86) (87). In our institutions the ROTEM® device is utilised; some information is summarised in Figures 1 and 2. VHA measure clot formation up to and including fibrinolysis in contrast to SLT, which document the beginning of fibrin formation when only 5% of total thrombin has been generated. VHA provide information regarding time to clot formation, clot strength and clot lysis; enabling different components of the coagulation cascade and their respective contribution to the clot kinetics to be assessed (85) (88) (89).

VHA have higher sensitivity for the detection of traumatic coagulopathy and provide results more rapidly than SLT (78) (90) (91) (92). In a study by Holcomb et al. (93) involving almost 2000 patients, Thromboelastography (TEG) was found to be superior to SLT across a number of parameters. The use of point of care (POC) rapid PT (rPT) devices can be utilised as an initial tool to assess coagulopathy but their utility remains controversial. A recent paper by Goodman et al, has suggested that POC rPT can be utilised as an alternative to r-TEG, reporting that rPT is cheaper and faster than r-TEG with similar diagnostic accuracy (94). In contrast, Davenport et al, report that although available quickly, the point of care rPT results are inaccurate with significant discrepancies to laboratory PT (78). The rPT may give an indication of the development of TIC and risk of subsequent massive transfusion but neglects the contribution of fibrinogen to clot strength (71). VHA have been incorporated into a number of trauma management guidelines and a number of trauma centres utilise targeted protocols in addition to or in place of fixed ratio MHP (64) (95) (96) (97). Inaba et al, have recently published a consensus statement based on expert opinion and extensive systematic literature review regarding VHA guided treatment triggers for blood product transfusion in severe trauma (81).

However, despite the growing evidence base to support the use of VHA in guiding blood product therapy in traumatic haemorrhage, data from randomised controlled studies is limited (57) (96) (98) (99) (100). A recent Cochrane Review concluded that there is an expanding evidence base that the application of VHA guided transfusion strategies can improve morbidity in bleeding patients (101). However, the quality of studies was low, the majority of trials were in cardiac surgical patients and further high quality studies in acute haemorrhage are required.

A recently published single centre randomised controlled trial reported significant reduction in blood product transfusion rates and improved survival with a TEG guided MHP (97). The multi-centre, prospective randomised controlled iTACTIC Trial (NCT:02593877) investigating the use of VHA in traumatic haemorrhage is currently recruiting in Europe. Patients randomised to the intervention arm will receive MHP resuscitation (1:1:1) with subsequent VHA (ROTEM® or TEG®) guided blood product and pro-coagulant factor administration; the control arm will receive the same 1:1:1 MHP resuscitation with subsequent blood product and pro-coagulant transfusion guided by standard laboratory tests. The primary outcome is proportion of patients alive and free of major haemorrhage at 24 hours. The trial will recruit about 400 patients and is aiming to complete at the end of 2017.

It has been suggested that there can be quality control and standardisation issues associated with point of care viscoelastic testing assays; with variability in test results between different devices, operators and centres (102) (103). It is important that institutions operating viscoelastic devices in the point of care setting should be involved in external quality assurance programmes (104) (105) (106).

Rapid Fibrinogen Assessment Utilising VHA:

Specific assays in both ROTEM® and TEG® are available to rapidly assess fibrinogen contribution to clot strength. In both assays the clot kinetics are assessed in the presence of a platelet inhibitor; FIBTEM (ROTEM®) – Cytochalasin D and Functional Fibrinogen [FF] (TEG®) - Abciximab. The FIBTEM and FF assays can be

utilised to rapidly identify those patients in whom hypo/dysfibrinogenaemia is contributing to on-going haemorrhage (55) (95) (107) (108). The FIBTEM and FF correlate well with standard laboratory measurements of fibrinogen concentration in a number of clinical situations (109) (110) (111) (112) (113).

There is good quality evidence to support the use of the FIBTEM assay as a marker of TIC and in predicting massive transfusion in severely injured trauma patients (90). There is increasing evidence to support the use of the FIBTEM assay as a strategy to decrease blood product transfusion in a variety of clinical settings (98) (114) (115) (116) (117). However, these findings have not been confirmed by high quality studies in the severely bleeding trauma patient.

To optimize capacity to correct coagulopathy rapidly, clot firmness amplitude results obtained at five minutes after clot formation (A5) can be used (55) (107) (118). A5 results have been found to correlate very well with maximum clot firmness (MCF) results in a number of clinical settings (118). Rapidly available real time results potentially permit targeted fibrinogen supplementation to those patients that need it rather than in a fixed-ratio MHP manner or in response to standard laboratory tests. The approach to fibrinogen replacement in our institution is demonstrated in Figures 3 and 4.

Cryoprecipitate for Fibrinogen Replacement:

Cryoprecipitate has been in use for more than 50 years and was originally developed as a treatment for patients with Haemophilia A (119). Each unit of cryoprecipitate is

prepared from 1 unit of FFP; thawed at 1-6^{o}C, centrifuged to remove the excess cryodepleted plasma, re-suspended in 30-40ml of residual plasma and refrozen at -18^{o}C. Although each unit of cryoprecipitate contains a high concentration of fibrinogen due to the small volume, the process recovers only 30% of fibrinogen from the plasma unit. In addition cryoprecipitate contains the other clotting factors - FVIII, vWF and FXIII. Cryoprecipitate is now almost exclusively used to replace fibrinogen in patients with acquired hypofibrinogenaemia – often in the setting of critical bleeding (120).

Cryoprecipitate use in severe trauma accounts for up to 30% of all units transfused (121) (122). There is widespread variability in the recommended dose of cryoprecipitate (ranging from 10 to 20 units) and little conformity between professional institutions (62). There is little high level evidence to support these dosing recommendations and reasons for this variability are twofold. Firstly, the concentration of fibrinogen in cryoprecipitate varies significantly between countries and institutions, ranging from 3-30g/l (62). In a Canadian study, cryoprecipitate units prepared in the same institution had fibrinogen concentrations ranging from 3.2 to 8.2g/l (123). The majority of regulatory authorities state that each unit of cryoprecipitate should contain at least 150mg of fibrinogen. Secondly and directly linked to the variability in fibrinogen per unit of cryoprecipitate, is the variable dose response to cryoprecipitate as determined by plasma fibrinogen levels. It is reported that the transfusion of 10U cryoprecipitate should increase the plasma fibrinogen by approximately 1g/l (124). However, in the trauma setting it has been reported that a dose of approximately 9U cryoprecipitate resulted in a mean increase in plasma fibrinogen of only 0.55g/l (125). The majority of guidelines recommend dosing of

cryoprecipitate in response to low plasma fibrinogen levels. This is impractical in the setting of severe bleeding where delays to effective transfusion of cryoprecipitate are compounded by the time taken to prepare and procure the requested units. A number of papers report the 'inappropriate' transfusion of cryoprecipitate i.e. not given in response to plasma fibrinogen levels (121) (122) (125) (126). It is likely that the delays in obtaining plasma fibrinogen results combined with time to prepare requested units, results in clinicians empirically ordering and transfusing cryoprecipitate on clinical grounds rather than as per published guidelines. The use of cryoprecipitate in traumatic haemorrhage varies widely between institutions and there are often significant delays to effective transfusion (54). The CRYOSTAT study has demonstrated that it is possible to transfuse cryoprecipitate early and empirically as part of a MTP, however, the median time to administration was still 60 minutes (69).

Cryoprecipitate (for fibrinogen replacement) has been withdrawn from use in many European countries due to safety concerns and has been replaced with Fibrinogen Concentrate (127) (128). A standard dose of cryoprecipitate is sourced from multiple donors, therefore potentially increasing the risk of pathogen transmission and transfusion related adverse events (129).

Cryoprecipitate is widely accepted as the standard of care for fibrinogen supplementation in severe haemorrhage; however, there is a lack of good quality evidence to support this strategy. It has been suggested, in view of the fact that cryoprecipitate is not virus-inactivated, is dosed in multiple units, with a lack of quality evidence to support its use and that there are potentially safer alternatives

available, it is unlikely that regulatory approval would be granted for its use today (62) (128).

Fibrinogen Concentrate for Fibrinogen Replacement:

There are a number of theoretical advantages to the use of FC; reduction in volume required, standard dose per vial, lack of variability in fibrinogen concentration, no requirement for ABO compatibility matching, viral inactivation, stored at room temperature, easily reconstituted and administered. However, in severe trauma there are no robust clinical trials demonstrating a survival or cost effectiveness benefit to the use of FC compared to cryoprecipitate (21) (63) (130) (131) (132).
There is increasing evidence supporting the important role of fibrinogen and the use of FC in other clinical situations with severe haemorrhage – cardiac surgery, obstetric haemorrhage and general surgery (133) (134) (135) (136) (137). Recent systematic reviews on the management of major haemorrhage and the use of fibrinogen supplementation suggest potential positive benefits but conclude more research is required (21) (138) (139). A Cochrane review evaluating the effectiveness of FC in severe haemorrhage reported six trials of moderate quality that were underpowered for mortality benefit detection but did demonstrate reduction in allogeneic transfusion requirements (140).

There is expanding observational evidence to support the use of FC in the setting of severe trauma and a number of studies have reported; increased clot strength, reduction in blood loss, reduced transfusion of allogenic blood products and reduction in mortality in patients treated with FC (96) (57) (98) (99) (141). Although

promising, the majority of publications are observational or retrospective cohort studies and do not provide high level evidence to support FC use in severe trauma.

A major concern regarding early fibrinogen replacement utilising FC is the potential for subsequent thromboembolic complications. This is of particular concern in severely traumatised patients who are at significant risk of this complication. A number of animal studies using models of traumatic coagulopathy provided initial safety data in favour of FC (142) (143) (144). Subsequently, a recently published pharmaco-vigilance study suggests that FC is not associated with increased thromboembolic complications; data from over 2.5 million grams of FC (approximately 600,000 standard doses of 4g) distributed over a 27 year period reported possible thromboembolic events in 28 cases (1 per 93,300 grams or 1 per 23,300 doses) (145). A comprehensive systematic review evaluating FC use in the perioperative setting concluded that there was no significant increase in thrombotic events in FC treated patients (146). Schochl et al. report in a cohort of severely injured trauma patients, that even after large doses of FC, subsequent plasma levels of fibrinogen did not exceed normal expected ranges and that there was no increased risk of thromboembolic complications (96).

Fibrinogen dosing:

The optimum dosing schedule of fibrinogen is controversial with widespread variability in recommendations from different professional bodies (62) (147) (148). European guidelines for massive haemorrhage in severe trauma recommend FC 3-4g or Cryoprecipitate 50mg/kg to restore fibrinogen levels (64). Taneka et al,

describe in detail the rationale behind cryoprecipitate and FC dosing (149). Collins et al, have published a theoretical model of fibrinogen dosing with plasma, cryoprecipitate and FC (65). Although this model is not designed for clinical use it does highlight the significant differences in volume of product potentially required to achieve effective fibrinogen supplementation. One of the potential advantages of using FC is the standardised fibrinogen concentration per vial (+/- 1g); making dosing and assessment of dose response easier than when utilising cryoprecipitate, which has a very wide variability in fibrinogen content per unit (131). Dosing strategies for FC using VHA have been suggested in the cardiac surgical patient population (150). In traumatic haemorrhage a few animal studies have suggested potential dosing strategies but there is a paucity of quality human data (151) (152).

Published data and local institutional data suggest that 1g of Fibrinogen (FC or Cryoprecipitate) will result in an increment of between 1.5 and 2mm in the FIBTEM assay (123) (150) (153). This is in line with published data suggesting that a 1g dose of fibrinogen will result in a plasma fibrinogen increment of 0.25g/l (56) (135) (154). Due to the variability in fibrinogen concentration in cryoprecipitate, including frequent loss of units to breakage during thawing, accurate dosing is more feasible with FC. Our local data supports the published literature in equating 1g of FC to between 3 and 5 single Units of cryoprecipitate (149). The recently completed but not yet published FIinTIC trial (NCT01475344) may provide guidance on appropriate FC dosing; this study utilised a weight based FC dosing strategy in the pre-hospital environment with fibrinogen levels on arrival to ED as the primary endpoint (155).

A recent publication from the AUVA Trauma Centre demonstrated that patients treated with FC did not have higher plasma fibrinogen levels than the control group of trauma patients not treated with FC in the post trauma phase (up to day 7) (156). Suggesting that despite relatively high doses of FC there is no 'overshoot' in plasma fibrinogen levels beyond expected levels subsequent to severe injury. All patients exhibited a rise in plasma fibrinogen levels post trauma that can be attributed to increased hepatic synthesis as part of the acute phase response to severe trauma. These findings are supported by the CRYOSTAT study; where there was no excessive rise in plasma fibrinogen levels or increased risk of thromboembolic complications with fibrinogen supplementation using cryoprecipitate therapy (69).

Fibrinogen Trials in Non-Traumatic Haemorrhage:

The use of Fibrinogen Concentrate has been extensively investigated in randomised controlled trials in patients with post-partum haemorrhage and those undergoing cardiac surgery. In the recently published FIB-PPH study, women with post-partum haemorrhage (PPH) were randomised into receiving either 2g FC or placebo, after clinical suspicion of significant PPH (>1.5L) (157). There was no difference in any of the primary outcomes between the two groups. However, the data presented showed that the mean plasma fibrinogen level in both groups was > 4g/l and therefore hypofibrinogenaemia was unlikely to be contributing to bleeding. The REPLACE study; investigating FC use in cardiac surgery has recently been published (158). This study randomised patients to FC or Placebo with a 5 minute bleeding mass of >60g after separation from cardio-pulmonary bypass. The study

reported increased allogenic blood product requirements in the FC arm. This was a surprising finding which was incongruent with the results of the pilot single centre studies and a full explanation is not clear. It is postulated that the low observed bleeding rates, use of the 5 minute bleeding mass (not routinely used in clinical practice), normal range plasma fibrinogen levels and a complex treatment algorithm all contributed to the unexpected results of the trial. These studies suggests that based on purely clinical indications it is difficult to predict which patients may benefit from fibrinogen supplementation and there is no benefit to fibrinogen supplementation in patients with normal fibrinogen levels.

A single “one-off” dose of additional fibrinogen supplementation “one size fits all approach” may not be appropriate and it is possible that fibrinogen replacement may better be guided by the degree of hypofibrinogenaemia to avoid potential under and over dosing. In a recent study investigating fixed dose fibrinogen concentrate supplementation in cardiac surgery – The Zero Plasma Trial (ZEPLAST), it was shown that a fixed dose of 6g FC reduced post-operative bleeding and blood product transfusion (159). However, subsequent data analysis revealed that a reduced dose of FC would have likely yielded the same results (160). It would seem to make intuitive sense to dose fibrinogen replacement based on degree of hypofibrinogenaemia.

Fibrinogen Trials in Traumatic Haemorrhage:

There is increasing recognition and good evidence to support of the importance of fibrinogen in effective clot formation in severe traumatic haemorrhage. The utility of

early fibrinogen replacement using FC and/or cryoprecipitate is gaining popularity but at the current time is not supported by high quality evidence (161). In the last decade there has been a vast amount of literature published regarding traumatic coagulopathy and transfusion strategies. However, the quality of evidence remains low as many of the reported studies contain significant methodological and statistical flaws (162).

The heterogeneous nature of injury pattern, the complex nature of traumatic coagulopathy and the geographical variation in clinical practice makes performing studies logistically challenging (163). Although individual patient randomised controlled trials in trauma present unique challenges to investigators, they are possible to perform successfully (48) (69). Two large multi-centre RCT's in bleeding civilian trauma patients have shown that outcomes can be improved with rapid haemostatic intervention. The CRASH-2 trial demonstrated a significant survival benefit in trauma patients treated with Tranexamic Acid within 3 hours of injury (164). Although the PROPPR study showed no difference in the primary outcome measures there was reduced death from haemorrhage and more rapid haemorrhage control in the intervention group (48).

A number of randomised controlled trials in severe traumatic haemorrhage investigating a VHA guided approach with use of Factor Concentrates are currently underway. The RETIC Trial (Reversal of TIC using Coagulation Factors or Fresh Frozen Plasma, NCT01545635) utilised a VHA (ROTEM®) algorithm to guide blood product transfusion. The intervention arm received FC and/or PCC in response to predefined (ROTEM®) values; the control arm received Plasma transfusion in

response to the same predefined (ROTEM®) values. Transfusion of PRBC, Platelets and TXA was the same in both arms and followed standard institutional clinical practise. The primary outcome measure being difference in MOF rates between the two groups. This trial has been terminated early after an interim analysis (100 patients) revealed possible harm to patients randomised to the Plasma arm. The STATA Trial (Strategy of Transfusion in Trauma Patients, NCT02416817) is comparing a VHA guided approach to a standard fixed ratio MHP. The intervention arm will receive Factor Concentrate (FC and PCC) and Platelet resuscitation guided by a VHA (ROTEM®) algorithm. The control arm will receive blood product transfusion as per a 1:1:1 MHP. The trial is aiming to recruit 200 patients with a primary outcome measure of SOFA scores during first 5 days of hospital admission and is expected to complete early in 2017.

Three randomised controlled blinded trials investigating early Fibrinogen Concentrate replacement in severe traumatic haemorrhage are currently underway or have recently completed; FiiRST (Fibrinogen in the initial Resuscitation of Severe Trauma, NTC02203968), E-FIT1 (Early Fibrinogen in Trauma, ISRCTN67540073) and PRooF-iTH (Pilot Randomised trial of Fibrinogen in Trauma Haemorrhage, NCT02344069). The FiiRST trial has been completed but not yet published. This pilot feasibility study randomised bleeding trauma patients to receive either 6g FC or Placebo on admission to the ED with a primary outcome measure being proportion of patients receiving intervention within 1 hour of hospital admission. The E-FIT1 trial currently recruiting in the UK is also enrolling patients based on clinical likelihood of significant haemorrhage with patients randomised to a single dose of 6g FC or placebo (in addition to standard MHP) as soon as possible after ED admission. The primary outcome measures are feasibility of administering FC within 45 minutes of

ED admission and the proportion of patients with at least one FibC level ≥ 2g/L during active haemorrhage. The PRooF-iTH trial currently recruiting in Copenhagen is slightly different from FiiRSt and E-FIT1. This study is again randomising patients with traumatic haemorrhage to receiving 60-70mg/Kg FC or placebo immediately and pre-emptively on arrival in the ED. The primary outcome is change in TEG FF Maximum Amplitude at 15 minutes after intervention. These trials will certainly address significant gaps in the evidence base surrounding FC use in severe trauma and help plan future studies.

The CRYOSTAT 2 Trial is currently in the planning stages based on the results of the pilot feasibility CRYOSTAT trial. CRYOSTAT 2 will be a large, international, multi-centre trial in severely bleeding trauma patients investigating fibrinogen supplementation using empiric and early cryoprecipitate as part of a MHP, with mortality as the primary outcome measure.

Fibrinogen Concentrate vs Cryoprecipitate in Traumatic Haemorrhage:

The large doses of cryoprecipitate utilised in traumatic haemorrhage place a significant strain on local blood banks in issuing requested units in a timely manner and on national blood supply agencies in maintaining and providing adequate stocks to support ABO requirements for individual blood banks. In addition the size and population distribution of countries like Australia makes supplying and maintaining adequate stocks of ‘fresh’ blood products in remote locations logistically challenging. The use of a lyophilised fibrinogen factor concentrate that has a long shelf life and is

easy to use has enormous implications for both large urban metropolitan areas and remote isolated communities.

However, randomised controlled trials are urgently required to investigate the haemostatic efficacy of cryoprecipitate compared to fibrinogen concentrate in traumatic haemorrhage. A recently published systematic review found sparse evidence comparing FC to cryoprecipitate and concluded that it was not possible to recommend one product over another in bleeding associated with acquired hypofibrinogenaemia (161). It is imperative that robust and clinically relevant studies are performed before widespread practice changes are implemented without a solid evidence base that would subsequently make performing such studies unfeasible (140) (165).

Recently published negative studies investigating the blind administration of fibrinogen supplementation in severe haemorrhage combined with the delays in fibrinogen replacement utilising MHP or standard laboratory tests potentially justify the conduct of a VHA guided trial. Although the inclusion criteria of the FiiRST, E-FIT1 and PRooF-iTH trials are robust and will identify patients with significant haemorrhage, it may not be possible to identify those patients in which hypofibrinogenaemia is contributing to on-going TIC associated haemorrhage. It is imperative to ensure that the appropriate product is given at the appropriate time in the appropriate quantity (157). It is likely that only sustained fibrinogen replacement throughout the resuscitation period in tandem with surgical haemorrhage control has the potential to impact on hypofibrinogenaemia and TIC (166). The use of a directed dosing strategy could inform dose response relationships for both FC and

cryoprecipitate in terms of plasma fibrinogen increments. Additionally it has been suggested that future trauma studies could use admission FIBTEM A5 measures to dose adjust fibrinogen replacement (69).

The Fibrinogen Early In Severe Trauma studY (FEISTY, NCT02745041) is a pilot, multi-centre, randomised controlled trial comparing FC to cryoprecipitate for fibrinogen supplementation in severe traumatic haemorrhage using accepted VHA triggers. This pragmatic study expanding on the currently utilised approach at the study sites; investigating the feasibility and efficacy of early fibrinogen supplementation is the first RCT comparing FC to Cryoprecipitate in traumatic haemorrhage. Adult patients with severe trauma and evidence of significant haemorrhage will be enrolled on arrival to the trauma unit and randomised to receiving fibrinogen supplementation with either FC or cryoprecipitate (Figure 5). The primary outcomes are time to administration of fibrinogen supplementation from time of ROTEM analysis (and clinical scenario) indicating fibrinogen supplementation is required and effects of fibrinogen supplementation on fibrinogen levels. Secondary outcomes include; blood product transfusion requirements, thromboembolic complications, hospital length of stay and mortality. A number of feasibility outcome measures will also be assessed. The study will take place in 4 major Queensland trauma centres and is expected to start recruiting in October 2016. The results of FEISTY will be used to design a larger and hopefully definitive multi-centre study with the aim of addressing patient centred outcomes such as allogenic blood product transfusion requirements and mortality. By performing a pilot multi-centre study it is hoped to identify logistical issues that could impact on the design and conduct of a

definitive study and potentially avoid the mistakes made in recently published FC studies (158).

Conclusion:

Whilst early fibrinogen supplementation with a concentrated product in severe traumatic haemorrhage is an attractive therapeutic option, there is currently inadequate high-level evidence to support its use. A number of on-going studies are currently investigating early fibrinogen replacement in severe trauma. Although the majority are pilot feasibility studies they will assist in planning larger definitive trials for the benefit of individual patients affected by trauma and for the community as a whole.

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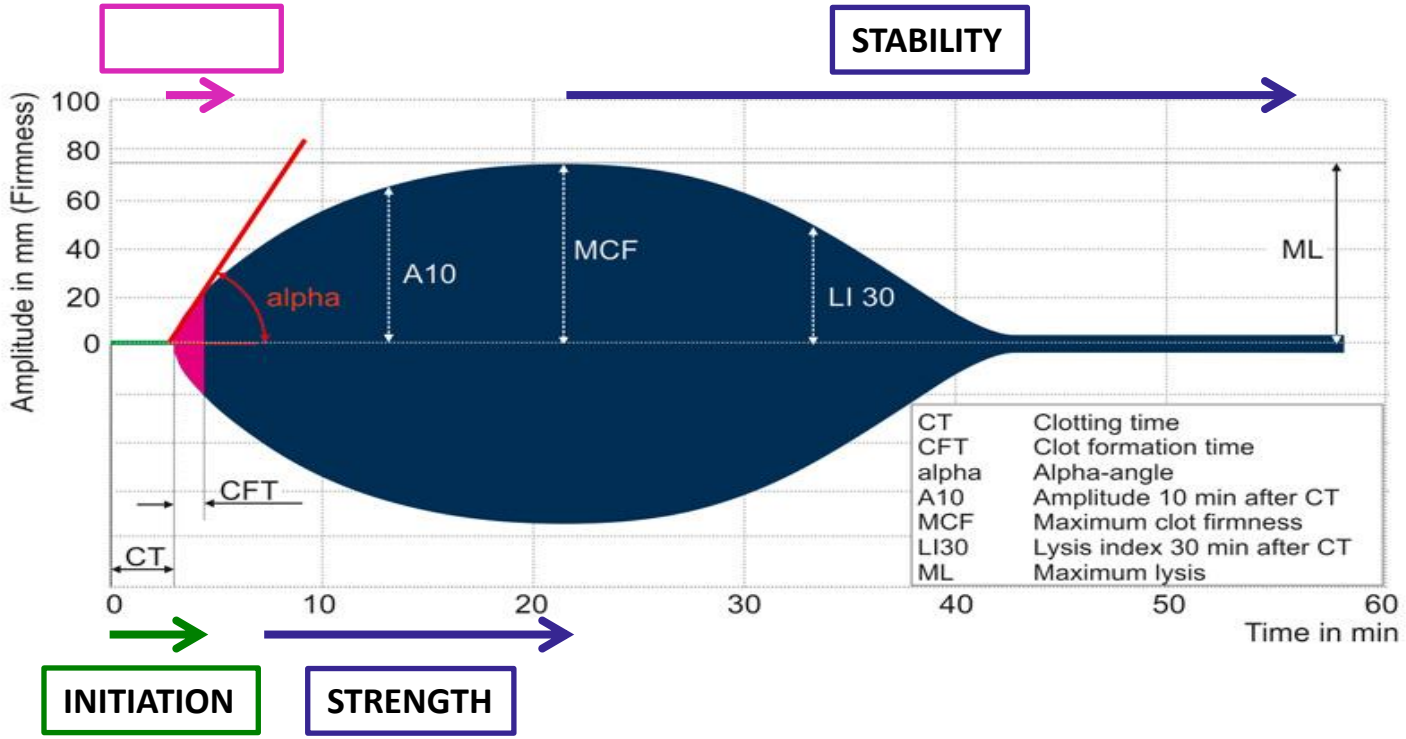
Figure 1. ROTEM Temogram
Figure 2. EXTEM and FIBTEM Analysis
Figure 3. GCUH ROTEM Guided Fibrinogen Replacement
Figure 4. Gunshot Wound Abdomen
Figure 5. FEISTY Randomisation and Intervention Flow Chart

Figure



PHASE	ROTEM Parameter	Coagulation Factor
INITIATION	CT - Clotting Time Measured in Seconds	Pro-Coagulant Factors Anti-Coagulant Factors
KINETICS	CFT - Clot Formation Time Measured in Seconds	Pro-Coagulant Factors Anti-Coagulant Factors Fibrinogen Platelets
STRENGTH	Amplitude after CT Measured in mm A5 – Amplitude after 5 mins A10 – Amplitude after 10 mins MCF – Maximum Clot Firmness	Fibrinogen Platelets FXIII
STABILITY	LI (Lysis Index/Residual Clot Firmness) Measured in % of MCF LI30 – 30 mins after CT ML – Maximum Lysis in % of MCF	Fibrinolytic Factors Fibrinolytic Inhibitors

Figure 2

EXTEM:

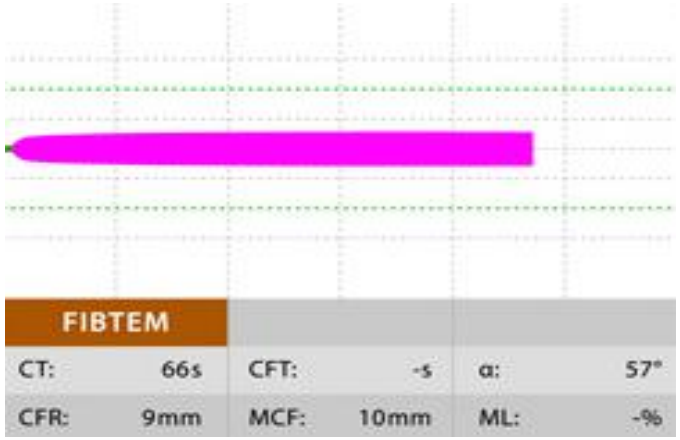
Activator: $CaCl_2$ + recombinant Tissue Factor

CT (Clotting Time) - Clotting Factors

Clot Amplitude (A5/A10/MCF) - Interaction of Fibrinogen and Platelets

↓ Clot Amplitude EXTEM + Normal FIBTEM = Poor Platelet Contribution

↑ CT + Normal FIBTEM = Factor Deficiency or Anticoagulants



FIBTEM:

Activator: $CaCl_2$ + recombinant Tissue Factor

Inhibition of Platelet Contribution by addition of Cytochalasin D

Clot Amplitude (A5/A10/MCF) - Fibrinogen Contribution

↓ Clot Amplitude FIBTEM = Fibrinogen Deficit or ↓ Fib Polymerisation

Figure 3

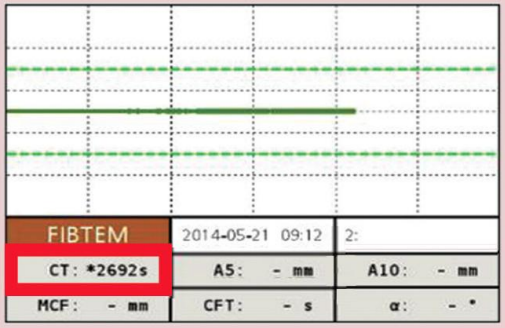
CRITICAL BLEEDING ROTEM TRANSFUSION ALGORITHM

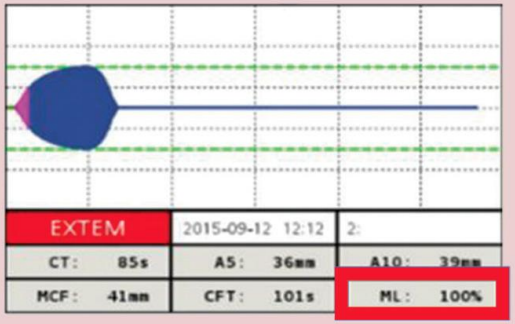
GOLD COAST UNIVERSITY HOSPITAL

Physiological Targets: Temp >36°C pH >7.2 iCa >1 mmol/L Hb>70g/L

STEP 1: HYPERFIBRINOLYSIS

1





FIBTEM CT > 600 sec

AND

EXTEM A5 < 35 mm

→ TXA 1g + FIB CONC 4g

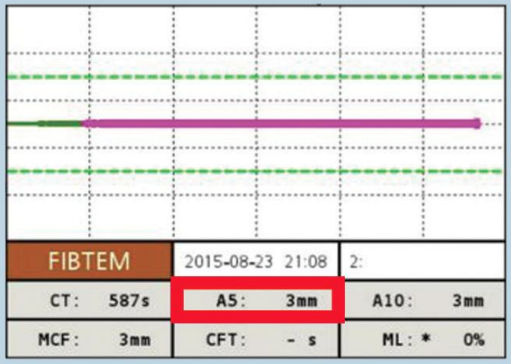
OR

ML% > 5%

→ TXA 1g

STEP 2: FIBRINOGEN

2



FIBTEM A5 ≤ 8 mm

→ FIB CONC 1g/25Kg BW

OR

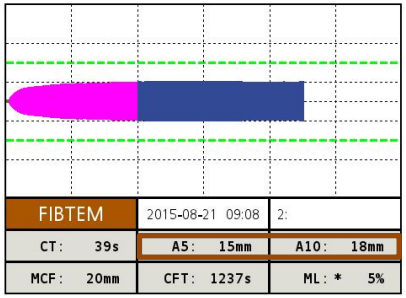
FIBTEM A5 ≤ 10 mm

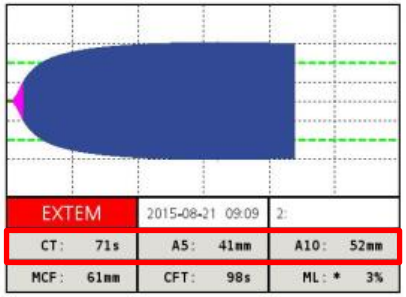
→ CRYO 1 Unit/5Kg BW

Figure 4

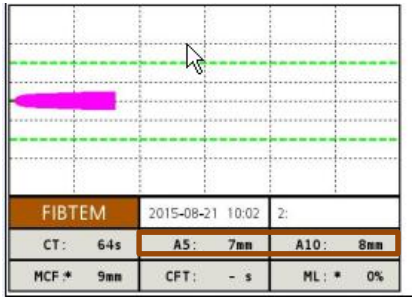
Fig 4. GSW Abdomen

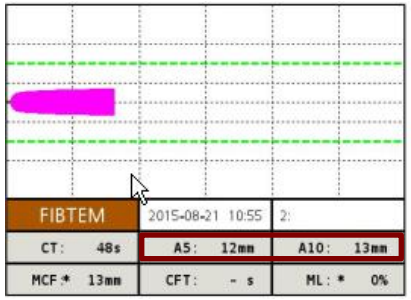
ED Arrival

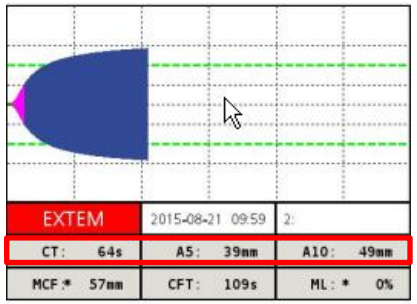


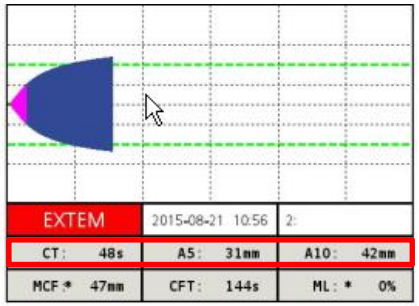


Operating Theatre

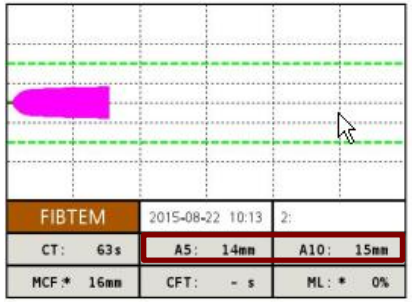


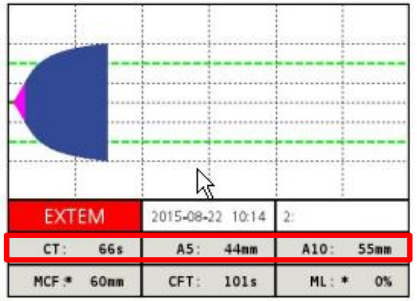






D1 ICU





ED Arrival: Hypotensive, FAST +ve, Lactate 9, BE -14 but Normal ROTEM and Standard Coagulation Tests
In OT: Visceral, vascular and renal tract injuries with significant haemorrhage
DCS: Abdomen Packed + Left Open
Blood product administration guided by ROTEM and utilising FC
ABG at end of case: pH 7.3, Lactate 3, BE -6
Total Transfusion 1st 24hrs: 8 PRBC, 4g FC, 10 Units Cryo, 1 Platelet, 1g TXA
SLT D1: Hb 104, PT 16, Plt 130, Fib 3
Definitive surgery completed 72 hours after admission